Influence of Phosphoramidites in Copper-Catalyzed Conjugate Borylation Reaction

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Beneficial influence of phosphoramidites in Cu-catalyzed conjugate borylation reaction

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Supporting information

Contents

1. Instrumentation and chemicals

All manipulations were carried out under nitrogen or argon atmosphere using Schlenk-type techniques, or in glove box. Solvents were dried by distillation from CaH_2 (DCM, hydrocarbons) or sodiumbenzophenone ketyl (THF), or were purchased from Fluka as anhydrous solvents and stored over molecular sieves. Bis(pinacolato)diboron was purchased from Lancaster, and it was used as received. All phosphorus ligands were prepared at DSM according to published procedures.[1]

The imines were prepared by published methods.[2] All other materials were purchased directly from standard chemical suppliers and used without further purification.
Gas chromatography analyses (GC) were performed using a Hewlett-Packard 6890 Chromatograph with flame ionization detector and an Agilent HP-5 (30 m x 0.32 mm, 0.25 micron) capillary column. Enantiomeric excesses were determined by HPLC using a Chiralpak IC column (250x4.6mm, 5 μm) and the following conditions:

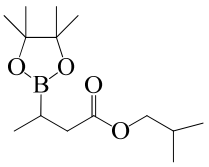
- For isobutyl crotonate, Eluent = hexane/DCM 96:4, 1 mL/min, T = 25 °C, Rt = 37.24, 42.89 min.

- For cinnamaldehyde and cinnamonitrile, Eluent = hexane/DCM 95:5, 5% DCM up to 20% in 60 min, 1 mL/min, T = 25 °C, Rt = 35.38, 38.99min for the aldehyde, R_t = 48.02, 50.25min.

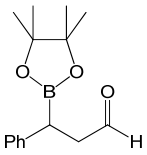
High performance liquid chromatography (HPLC) was carried out using a Shimadzu Class VP model equipped with an autosampler and UV detector. Chiralpak AD-H column (dimensions 250 x 4.6 mm) or Chiralpak OD-H column (dimensions 250 x 4.6 mm) were used to determine enantiomeric excesses.
Deuterated chloroform ($CDCl_3$) was used as solvent for routine NMR measurements. NMR spectra were obtained using a Varian Gemini 300, a Varian Mercury 400 or a Bruker Avance 300 spectrometer. ^1H NMR (δ) chemical shifts were referenced to the chemical shift of residual solvents resonances.

2. β-Boration of isobutyl crotonate, cinnamaldehyde and cinnamonitrile

The 96 reactions were carried out in 5mL vials. For the reaction at room temperature (with isobutyl crotonate and cinnamonitrile), the vials were kept within the glovebox in a rack placed on an orbital shaker. For the reaction at 70°C, the vials were placed within Premex A96-Multi Reactor where the temperature could be raised to the desired value and the stirring was done via an individual magnetic stir bar in each vessels. A Zinsser Lissy liquid handling robot was used to prepare the 96 reaction mixtures from stock solutions of the different components. Stock solutions in THF were prepared of the CuOTf·4CH_3CN (0.05 M), of the ligands (0.1 M if monodentate, 0.05 M if bidentate), of the isobutyl crotonate (1.786 M, the volume of the substrate and the volume of the THF were considered to be additive), of the cinnamaldehyde (1.908 M, the volume of the substrate and the volume of the THF were considered to be additive), of the cinnamonitrile (1.908 M, the volume of the substrate and the volume of the THF were considered to be additive), and of a mixture of *t*BuONa, B_2pin_2, and MeOH (0.0107 M, 0.4 M, and 0.7 M, respectively). The reactions vessels of the multi reactor were filled with the stock solutions of the reaction components in the following order. First, stock solutions of CuOTf·4CH_3CN (0.1 mL of 0.05 M, 0.005 mmol) were added, followed by the stock solutions of the ligands (0.1 mL of 0.1 M if monodentate or 0.05 M if bidentate, 0.01 mmol if monodentate or 0.005 mmol if bidentate), then the reaction mixture was stirred for 10 minutes. Stock solution of a mixture of *t*BuONa, B_2pin_2, and MeOH (0.7 mL of 0.0107 M, 0.4 M, and 0.7 M; 0.0075 mmol, 0.28 mmol, 0.5 mmol, respectively) was added, followed by the stock solutions of the isobutyl crotonate (140 μL, 1.786 M, 0.25 mmol), the cinnamaldehyde (131 μL 1.908 M, 0.25 mmol), the cinnamonitrile (131 μL 1.908 M, 0.25 mmol). The reaction mixtures of the ester and the nitrile were stirred at room temperature for 4 hours, the reaction mixtures of the aldehyde were stirred at 70 °C for 4 hours. After the reaction analytical samples were immediately prepared from the reaction mixtures, and the samples were analyzed by GC-MS, and chiral HPLC.



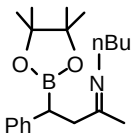
^{1}H NMR (400 MHz, $CDCl_3$) = δ 3.87 (m, 2H), 2.41 (dd, J=16.8 Hz, J=7.6 Hz, 1H), 2.38 (dd, J=16.8 Hz, J=7.6 Hz, 1H), 1.82 (m, 1H), 1.45 (q, J=7.2 Hz, 1H), 1.26 (s, 6H), 1.21 (s, 6H), 1.02 (d, J=7.2 Hz, 3H), 0.95 (d, J= 6.8, 6H).



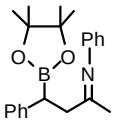
^{1}H NMR (300 MHz, $CDCl_3$) = δ 9.75 (s, 1H), 7.70 – 7.05 (m, 5H), 2.64-2.45 (m, 2H), 1.33 (m, 1H), 1.20 (s, 12H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) = δ 202.8, 127.4, 125.5, 124.6, 83.3, 47.9, 25.2, 24.9, 14.4. ^{11}B NMR (96.27 MHz, $CDCl_3$) = δ 33.4

3. β-Boration of α,β-unsaturated imines

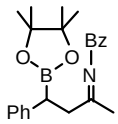
The reactions were carried out in a Carousel Multi Reactor connected to a Schlenk line. Stock solutions in THF were prepared of $CuOTf{\cdot}4CH_3CN$ (0.02 M), of the ligands (0.04 M), and of a mixture of the imines, *t*BuONa, B_2pin_2, and MeOH (0.5 M, 0.0155 M, 0.555 M, and 1 M, respectively). The reactions vessels of the multi reactor were filled with the stock solutions of the reaction components in the following order. First, stock solution of the $CuOTf{\cdot}4CH_3CN$ (0.25 mL of 0.02 M, 0.005 mmol) was added, followed by the stock solutions of the ligands (0.25 mL of 0.04 M, 0.01 mmol), then the reaction mixture was stirred for 10 minutes. Stock solution of a mixture of the imine, *t*BuONa, B_2pin_2, and MeOH (0.5 mL of 0.5 M, 0.015 M, 0.555 M, and 1 M; 0.25 mmol, 0.0075 mmol, 0.28 mmol, 0.5 mmol, respectively) was added. The reaction mixtures were stirred at room temperature for 4 hours. After the reaction analytical samples were immediately prepared from the reaction mixtures, and the samples were analyzed by ^{1}H-NMR and chiral HPLC.



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.19 (m, 5H), 3.54 (t, *J* = 8 Hz, 2H), 3.03 (dd, *J* = 20, 8 Hz, 1H), 2.81 (dd, *J* = 20, 8 Hz, 1H), 2.65 (m, 1H), 2.18 (s, 3H), 1.43 (m, 2H), 1.24 (m, 14H), 0.88 (t, *J* = 8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 160.99, 134.62, 129.00, 128.35, 127.07, 87.76, 61.72, 52.15, 32.70, 29.73, 27.79, 21.21, 13.98; ^{11}B NMR ($CDCl_3$, 128.3 MHz) δ 21.72.



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.19 (m, 10H), 3.09 (m, 1H), 2.91 (m, 1H), 2.64 (m, 1H), 2.19 (s, 3H), 1.32 (m, 12H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 169.99, 148.93, 145.35, 132.77, 132.42, 131.39, 131.08, 130.11, 129.46, 87.27, 52.63, 29.53, 25.62, 19.67; ^{11}B NMR ($CDCl_3$, 128.3 MHz) δ 21.38



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.07 (m, 10H), 4.80 (dd, *J* = 12 Hz, 1H), 4.65 (dd, *J* = 12 Hz, 1H), 3.03 (dt, *J* = 20, 8 Hz, 1H), 2.77 (dd, *J* = 20, 8 Hz, 1H), 2.25 (m, 1H), 2.10 (s, 3H), 1.19 (m, 12H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 167.90, 139.54, 136.63, 136.24, 132.94, 128.37, 126.65, 126.34, 125.7, 88.16, 51.19, 36.72, 29.40, 22.17, 13.25; ^{11}B NMR ($CDCl_3$, 128.3 MHz) δ 21.18

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